Claims

What is claimed is

1. Use of an inhibitor of a PDE enzyme for the preparation of a medicament for stimulating ovarian follicular growth in a female.

2. Use according to claim 1, wherein the patient is undergoing ovulation induction.

3. Use according to claim 1 or 2, wherein the patient is undergoing controlled ovarian hyperstimulation.

4. Use according to claim 1, 2 or 3, wherein the medicament is for simultaneous, separate or sequential administration with FSH, or an agent having FSH activity, or an agent that stimulates endogenous FSH release.

5. Use according to claim 1, 2 or 3, wherein the medicament is for simultaneous, separate or sequential administration with FSH.

6. Use according to claim 1, 2 or 3, wherein the medicament is for simultaneous, separate or sequential administration with an agent having FSH activity, or an agent that stimulates endogenous FSH release.

7. Use according to any one preceding claim, wherein the medicament is administered starting at or about day 2 to 3 after menses.

8. Use according to any one preceding claim, wherein the medicament is administered daily until follicular growth is sufficient, when an ovulation triggering dose of hCG is administered.

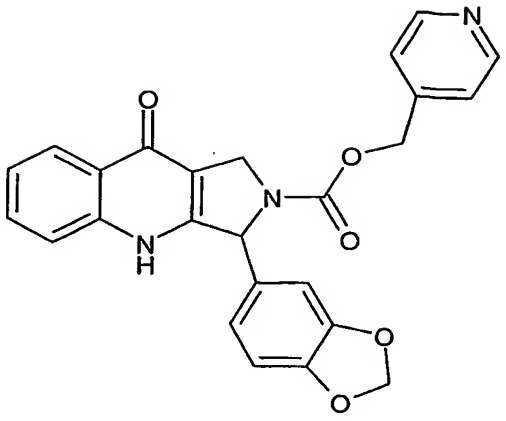
9. Use according to claim 8, wherein the ovulation triggering dose of hCG is 5,000-10,000 IU.

10. Use according to any one preceding claim, wherein the medicament is administered with FSH, and wherein the dose of FSH is less than the dose required in the same patient in the absence of the PDE inhibitor, in order to achieve the same result in terms of follicular growth.

11. Use according to any one preceding claim, wherein the PDE inhibitor is an inhibitor of at least one PDE type selected from 1, 5 and 6.

12. Use according to any one preceding claim, wherein the PDE inhibitor is selected from: 5-[2-ethoxy-5-(4-methyl-1 -piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil); Zaprinast; dipyridamole; 5-(2-ethoxy-5-morpholinoacetylphenyl)-1 -methyl-3-n-propyl-1,6-dihydro-7H-20 pyrazolo[4,3-d]pyrimidin-7-one; 3-ethyl-5-[5-(4-ethylpiperazin- 1 -ylsulphonyl)-2-n-propoxyphenyl]-2-(pyr- idin-2-yl) methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridi- n-3-yl]-2-(pyridin-2-yl) methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; (+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7 H-pyrazolo[4 ,3-d] pyrimidin-7-one; 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-[2-iso-butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-[2-ethoxy-5-(4-ethylpiperazin-1 -ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1 -isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2 ,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one; (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(- 3,4-methylenedioxyphenyl)pyrazino[2',1 ':6,1]pyrido[3,4-b]indole-1,4-dione (Tadalafil; IC-351); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo [5,1 -f][1,2,4]triazin-4-one (vardenafil); 4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1 -[4-

[(1,3-benzodioxol-5-ylmethyl)amiono]-6-chloro-2-quinozolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-[4,5]imidazo[2,1-b]purin-4(3H)one; furaziocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]-imidazo[2- ,1 -b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6- carboxylate; 3-acetyl-1 -(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl)propoxy)-3-(2H) pyridazinone; 1-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro- 7H-pyrazolo (4,3-d)pyrimidin-7-one; 1 -[4-[(1,3-benzodioxol-5-yl methyl)amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516; Pharmaprojects No. 5051; Pharmaprojects No. 5064; Pharmaprojects No. 5069; GF-196960; E-8010 and E-4010; Bay-38-3045 & Bay-38-9456; Vinpocetine; SCH-51866; SCH-59498; (6a*R*,9a*S*)-2-(Biphenylylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3(phenylmethyl)cyclopent [4,5] imidazo-[2,1-*b*]purin-4(3*H*)-one; 5'-Methyl-2'(biphenylylmethyl)-3'-(phenylmethyl) spiro[cyclopentane-1,7'(8'*H*)-[3*H*]imidazo[2,1-*b*]purin]-4(5'*H*)-one; (6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(phenylethynyl)-3-(phenylmethyl)cyclopent [4,5] imidazo[2,1-*b*]-purin-4(3*H*)-one; dipyridamole, AWD-12-171 and AWD-12-217; BMS-341400; UK-343,664; 5E-3623, 5E-3569, 5E-3657, E4021; KS-505a; YC-1; IDDB reference number 323951; WIN-61691; FR226807; IDDB references 461317, 462503, 461321, 461324, 466146; pyridine-4-ylmethyl 3-(1,3-benzodioxol-5-yl)-9-oxo-1,3,4,9 tetrahydro-2H-pyrrolo [3,4-b] quinoline-2-carboxylate:



13. Use according to any one preceding claim, wherein the PDE inhibitor is selected from Sildenafil; Zaprinast; Dipyridamole; (6a*R*,9a*S*)-2-(Biphenylylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3(phenylmethyl)cyclopent [4,5] imidazo-[2,1-*b*]purin-4(3*H*)-one; and 5'-Methyl-2'(biphenylylmethyl)-3'-(phenylmethyl) spiro[cyclopentane-1,7'(8'*H*)-[3*H*]imidazo[2,1-*b*]purin]-4(5'*H*)-one.

14. Use according to any one of claims 1 to 11, wherein the PDE inhibitor is Zaprinast.

15. Use according to any one of claims 1 to 11, wherein the PDE inhibitor is Sildenafil.

16. Use according to any one of claims 1 to 11, wherein the PDE inhibitor is Tadalafil.

17. Use according to any one of claims 1 to 11, wherein the PDE inhibitor is a selective inhibitor of PDE 1 and PDE 5.

18. Use according to any one of claims 1 to 11, wherein the PDE inhibitor is a selective inhibitor of PDE 1.

19. Use according to any one of claims 1 to 11, wherein the PDE inhibitor is a selective inhibitor of PDE 5.

20. A method of increasing follicle maturation comprising treating a female with a composition comprising a phosphodiesterase (PDE) inhibitor in an amount effective to stimulate follicular maturation.

21. A method of increasing oocyte maturation comprising treating an oocyte *in vitro* with a composition comprising a PDE inhibitor in an amount effective to cause oocyte maturation.

22. A method according to claim 20 or 21, wherein the composition comprises at least one PDE 4 inhibitor.

23. A method according to claim 20 or 21, wherein the composition comprises at least one PDE 4 inhibitor selected from the group consisting of Piclamilast, Roflumilast, Ariflo, Filaminast, Mesopram, D4418, Arofylline, and CL1044.

24. A method according to claim 20 or 21, wherein the composition comprises at least one PDE 4 inhibitor and one other PDE inhibitor selected from the group consisting of a PDE 1 inhibitor, a PDE 7 inhibitor, a PDE 9 inhibitor, a PDE 10 inhibitor, and a PDE 11 inhibitor.

25. A method according to claim 20 or 21, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

26. A method according to claim 22, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

27. A method according to claim 23, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

28. A method according to claim 24, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

29. A method according to claim 20 or 21, wherein the method further comprises treatment with FSH.

30. A method according to claim 20 or 21, wherein the method further comprises administering FSH and at least one non-FSH gonadotropin hormone.

31. A method according to claim 30, wherein the non-FSH gonadotropin hormone is luteinizing hormone.

32. A method according to claim 30, wherein the non-FSH gonadotropin hormone is chorionic gonadotropin.

33. A method according to claim 20 or 21, wherein the method comprises administering a stimulator, agonist or adjuvant of FSH alone in combination with a PDE 4 inhibitor.

34. A method according to claim 33, wherein the stimulator of FSH is selected from the group consisting of Letrozole, Anastrozole, and Vorozole.

35. A method according to claim 25, wherein the PDE inhibitor and the gonadotropin hormone are administered concurrently.

36. A method according to claim 25, wherein the PDE 4 inhibitor and FSH are contained in a single vial as a mixture.

37. A vial containing a single dose of a mixture of PDE 4 inhibitor and FSH.

38. A method according to claim 25, wherein the PDE inhibitor is administered prior to the gonadotropin hormone treatment.

39. A method according to claim 25, wherein the PDE inhibitor is administered after the gonadotropin hormone treatment.

40. A method according to claim 25, wherein the FSH is administered at a dosage range of about 5 to 450 IU/day.

41. A method according to claim 25, wherein the FSH is administered at a dosage range of about 5 to 75 IU/day.

42. A method according to claim 20, wherein the method comprises administering to the female a composition comprising at least one PDE 4 inhibitor and an exogenous FSH hormone.

43. A method according to claim 42, wherein the exogenous FSH hormone is a recombinant FSH hormone.

44. A method according to claim 42, wherein the exogenous FSH hormone is urinary FSH hormone.

45. A method according to claim 42, wherein the PDE 4 inhibitor is administered in a dose of about 0.05 mg/day to about 5 mg/day.

46. A method according to claim 42, wherein the PDE 4 inhibitor is administered in a dose of about 10 mg/day to about 200 mg/day.

47. A method according to claim 42, wherein the FSH is administered in a dosage range of 5 IU FSH/day to 75 IU FSH/day.

48. A method according to claim 42, wherein the FSH is administered in a dosage of 150 IU FSH per day.

49. A method according to claim 42, wherein the FSH is administered in a single dose.

50. A method according to claim 42, wherein the FSH is administered in multiple doses.

51. A method according to claim 42, wherein the FSH is administered intramuscularly or subcutaneously.

52. A method according to claim 42, wherein the FSH is administered between day 2 and day 14 of the menstrual cycle of the female.

53. A method according to claim 42, wherein the FSH is administered for 7 to 12 consecutive days.

54. A method according to claim 42, wherein the method further comprises suppression of endogenous FSH and LH production in the female prior to administration of the PDE 4 inhibitor and the FSH hormone.

55. A method according to claim 54, wherein suppression of endogenous FSH and LH production is effected by the administration of GnRH or an analog thereof to the female.

56. A method according to claim 54, wherein GnRH, or an analog thereof, is administered to the female for 30 days prior to the administration of the at least one PDE 4 inhibitor and the exogenous FSH hormone.

57. A method according to claim 55, wherein GnRH, or an analog thereof, is administered in a dosage range of from about 0.25 mg to about 3 mg GnRH on a daily basis.

58. A method according to claim 42, wherein the female produces 4 or more oocytes that are harvestable.

59. A method according to claim 58, further comprising the step of harvesting the oocytes 12 days after the PDE 4 inhibitor and the FSH were first administered.

60. A method according to claim 59, further comprising the step of fertilizing the harvested oocytes in vitro, culturing the harvested, fertilized oocytes to the 4-8 cell stage, and transferring the 4-8 cell stage fertilized oocytes to the uterus of a female.

61. A kit for the treatment of infertility, the kit comprising

a first composition comprising at least one PDE 4 inhibitor in a pharmaceutically acceptable formulation, and

a second composition comprising FSH in a pharmaceutically acceptable formulation.

62. A kit according to claim 61, wherein the kit comprises urinary FSH or recombinant FSH.

63. A kit according to claim 62, wherein the kit comprises human FSH.

64. A kit according to claim 61, wherein the FSH of the kit is provided in a unit dose of between about 5 IU FSH and about 75 IU FSH.

65. A kit according to claim 61 further comprising a third composition comprising LH in a pharmaceutically acceptable formulation.

66. A kit according to claim 65, wherein the LH of the kit is provided in a unit dose of between about 75 IU LH and about 150 IU LH.